UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,759	01/30/2002	Adam Lerner	701586/50174-DIV	8480

50607 7590 10/31/2007

RONALD I. EISENSTEIN
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/060,759	LERNER, ADAM	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1-7 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-7 and 15-16 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 8/6/2007 has been received and entered into the application. Accordingly, claim 1 has been amended and claim 16 has been added.

Applicants' arguments, filed 8/6/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

Per the Response to Election/Restriction filed 4/23/2004, Applicant elected as the species of Type 4 cyclic adenosine monophosphate phosphodiesterase inhibitor the compound XX5, namely Ro-1724 ((4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone)(Ro-20-1724)). As indicated in the previous Office Action, claim 15, which is limited to the treatment of chronic lymphocytic leukemia comprising administering a formulation comprising 4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone, is allowable over the prior art.

However, upon further consideration, new 35 U.S.C. § 112, 1st Paragraph rejections are herein applied to generic claims 1-7 and 16, which are not limited to a specific inhibitor of Type 4 cyclic adenosine monophosphate phosphodiesterase.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude

extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

The instant claims recite administration of "an inhibitor that specifically inhibits Type 4 adenosine monophosphate phosphodiesterases" (claim 1). With respect to such "specific" inhibition, the specification, at page 4, lines 6-13, describes compounds that specifically inhibits Type 4 adenosine monophosphate phosphodiesterases as those compounds that inhibit Type 4, but not Type 1 or Type 3 phosphodiesterases. It is further taught that "background level inhibition of Type 1 or 3 phosphodiesterases" is permitted within this definition. However, inhibition of Type 4 to a greater extent that Type 1 and/or Type 2 phosphodiesterases is not within the meaning of an inhibitor that *specifically* inhibits Type 4 adenosine monophosphate phosphodiesterases. Only two specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase are disclosed in the specification, namely rolipram (4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone) and XX5 (4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone) (page 7, lines 2-9). No other specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase are contemplated or described in the specification.

Accordingly, Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from the express identification of the compounds rolipram and XX5, which would provide adequate written description of the genus of compounds capable of specifically inhibiting Type 4 adenosine monophosphate phosphodiesterases.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating CLL with rolipram or XX5, does not reasonably provide enablement for treating CLL with any and all specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to the treatment of chronic lymphocytic leukemia comprising administering a specific inhibitor of Type 4 adenosine monophosphate phosphodiesterase.

Relative skill of those in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

State and predictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In*

re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a broad genus of compounds being used to treat the same cancer.

The breadth of the claims: The claims are extremely broad insofar as they disclose the treatment of chronic lymphocytic leukemia with a genus of compounds that is only defined with respect to its in vitro activity (*i.e.*, specific inhibition of Type 4 PDE).

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat CLL with the broad genus of compounds contemplated by the claims, particularly in humans. The direction concerning treating cancer is found in the specification at pages 15-23, which provides cellular assays for determining the cell growth inhibitory effect of the claimed compounds. Only rolipram and XX5 were actually tested in these assays. Applicant describes formulations at pages 7-11. No doses required to practice the invention are described. Since rolipram and XX5 have only been demonstrated to induce apoptosis of CLL cells *in vitro*, how is the skilled physician to know what dose to use for each of the compounds contemplated for administration in the instant claims? There are no guidelines for determining the doses needed to treat CLL *via* enteral administration (claims 2-3) or parenteral administration (claim 4). There is

an *in vitro* cellular assay for induction of apoptosis of CLL cells described in pages 15-23 but it is unclear if this assay correlates to the induction of apoptosis in such cells with any and all specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase as only rolipram was tested. There are no working examples of treatment of CLL in animals or man.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the full scope of the instantly claimed genus of compounds (*i.e.*, specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase) could be predictably used as a treatment for CLL in human patients as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).
In the instant case, Applicant has presented a general idea that because rolipram and XX5 induce apoptosis of CLL cells in vitro, then all specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase must therefore, *a priori*, be useful in the treatment of CLL in human patients. However, the claims encompass a multitude of compounds, defined only by their inhibition of an enzyme, having a plethora of chemically and biologically distinct substituents.

It is evident that a very small percentage of the claimed compounds were actually tested (for induction of apoptosis *in vitro*) by Applicant and both of the tested compounds were already

known in the art as specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase. Applicant has provided no means for the skilled artisan to synthesize and test other compounds for specific inhibition of Type 4 adenosine monophosphate phosphodiesterase. Further, inhibition of an enzyme *in vitro* is not generally predictive of such activity *in vivo* (due to possible metabolic degradation of the active compound *in vivo*, limited bioavailability, etc.). Considering the broad scope of the claimed invention, it would take undue experimentation for the skilled artisan to synthesize and identify specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase, determine whether such inhibitors are active *in vitro*, determine whether compounds active *in vitro* are active *in vivo*, and finally evaluate whether a compound active in an *in vivo* model of CLL is effective in the treatment of human patients.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

October 22, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER